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(54) AZABICYCLIC CARBAMATES AND THEIR USE AS ALPHA-7 NICOTINIC ACETYLCHOLINE RECEPTOR AGONISTS

AZABIZYKLISCHE CARBAMATE UND IHRE ANWENDUNG ALS ANTAGONISTEN DES ALPHA-7 NIKOTINISCHEN ACETYLCHOLIN REZEPTORS

CARBAMATES AZABICYCLIQUES ET LEUR UTILISATION COMME AGONISTES DES RECEPTEURS NICOTINIQUES ALPHA-7 DE L'ACETYLCHOLINE

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(56) References cited:
WO-A-96/08468
US-A- 5 988 429

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EP 1 282 620 B1

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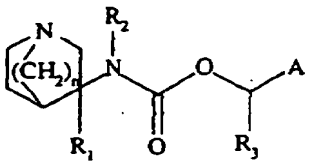
Description

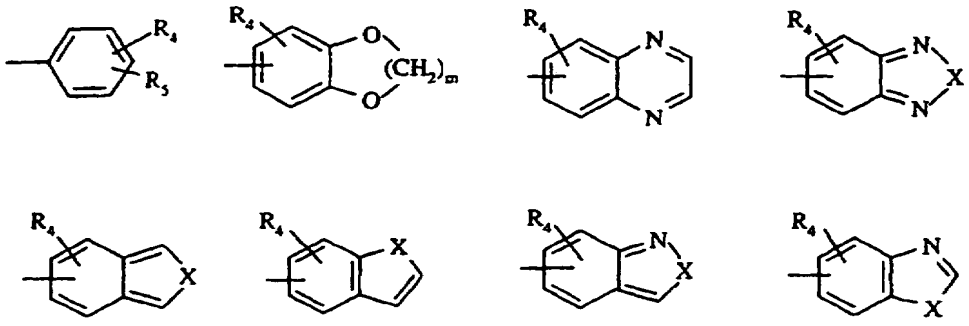
[0001] The present invention relates to novel azabicyclic carbamates, their preparation, their use as pharmaceuticals and pharmaceutical compositions containing them.

[0002] More particularly the invention provides a compound of formula I



I

wherein n is 1 or 2, R_1, R_2 and R_3, independently, are hydrogen or (C_{1-4})alkyl and A is a group of formula



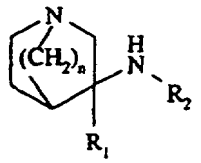
wherein m is 1, 2 or 3, X is O, S, NH or CH_2 and R_4 and R_5, independently, are hydrogen, halogen, hydroxy, (C_{1-4})alkyl, (C_{1-4})alkoxy, (C_{1-4})alkylthio, (C_{1-4})alkylamino, nitro, trifluoromethyl or phenyl, in free base or acid addition salt form.

[0003] Halogen denotes fluorine, bromine, chlorine or iodine.

[0004] Any alkyl, alkoxy and alkylthio groups are branched or straight chain groups. They are preferably methyl, methoxy or methylthio groups.

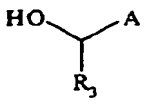
[0005] On account of the asymmetrical carbon atom(s) present in the compounds of formula I and their salts, the compounds may exist in optically active form or in form of mixtures of optical isomers, e.g. in form of racemic mixtures. All optical isomers and their mixtures including the racemic mixtures are part of the present invention.

[0006] In a further aspect, the invention provides a process for the production of the compounds of formula I and their salts, comprising the step of reacting a compound of formula II



II

wherein n, R_1 and R_2 are as defined above, with a compound of formula III

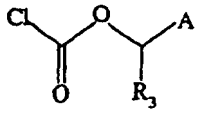


III

wherein R_3 and A are as defined above, and N, N'-carbonyldiimidazole or di(N-succinimidyl)carbonate, and recovering the resulting compound of formula I in free base or acid addition salt form.

[0007] According to a preferred embodiment, in a first step the compound of formula III is reacted with N, N'-carbonyldiimidazole, and the resulting compound is reacted with the compound of formula II.

[0008] Alternatively, the compound of formula II can be reacted with a compound of formula IV



IV

wherein R_3 and A are as defined above.

[0009] The reactions can be effected according to conventional methods, e.g. as described in the examples.

[0010] Working up the reaction mixtures according to the above processes and purification of the compounds thus obtained may be carried out in accordance to known procedures.

[0011] Acid addition salts may be produced from the free bases in known manner, and vice versa.

[0012] Compounds of formula I in optically pure form can be obtained from the corresponding racemates according to well-known procedures. Alternatively, optically pure starting materials can be used.

[0013] The starting materials of formula II, III and IV are known or may be obtained from known compounds, using conventional procedures.

[0014] Compounds of formula I and their pharmaceutically acceptable acid addition salts, hereinafter referred to as agents of the invention, exhibit valuable pharmacological properties when tested in vitro and in animals, and are therefore useful as pharmaceuticals.

[0015] In particular, the agents of the invention are α7 nicotinic acetylcholine receptor (nAChR) agonists.

[0016] In functional assays, the agents of the invention display high affinity at the α7 nAChR as shown in the following tests:

a) A functional assay for affinity at human α7 nAChR is carried out with a rat pituitary cell line stably expressing the human α7 nAChR. As a read out, the calcium influx upon stimulation of the receptor is used. In this assay, agents of the invention exhibit pEC_{50} values of about 5 to about 8.

b) To assess the activity of the agents of the invention on the human neuronal nAChR α4β2, a similar functional assay is carried out using a human epithelial cell line stable expressing the human α4β2 subtype. In this assay, agents of the invention show selectivity for the α7 nAChR subtypes.

c) To assess the activity of the compounds of the invention on the "ganglionic subtype" and the muscle type of nicotinic receptor, similar functional assays as described under a) are carried out with a human epithelial cell line stably expressing the human ganglionic subtype or a cell line endogenously expressing the human muscle type of nicotinic receptors. In these assays, agents of the invention display no or little activity on the ganglionic and muscle type of nicotinic receptor subtypes.

[0017] In the model of mice showing sensory gating deficit (DBA/2-mice) described by S. Leonard et al. in Schizophrenia Bulletin 22, 431-445 (1996), the agents of the invention induce significant sensory gating at concentrations of about 10 to about 40 μM.

[0018] The agents of the invention are therefore useful for the treatment of psychotic disorders such as schizophrenia, mania, depression and anxiety, and for the treatment of neurodegenerative disorders such as senile dementia, Alzheimer's disease and other intellectual impairment disorders, such as attention deficit hyperactivity disorders (ADHD); Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis and multiple sclerosis. The usefulness of α7 nAChR agonists in neurodegeneration is documented in the literature, e.g. in Wang et al., J. biol. Chem. 275, 5626-5632 (2000).

[0019] For the above-mentioned indications, the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.01 to about 100, preferably from about 0.1 to about 50 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 1 to about 500, preferably from about 5 to about 300 mg of an agent of the invention conveniently administered, for example, in divided doses up to four times a day or in

sustained release form.

[0020] The agent of the invention may be administered by any conventional route, in particular enterally, preferably orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injectable solutions or suspensions.

[0021] The preferred compound is the stereoisomer of the (1-aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid 1-(2-fluorophenyl)-ethyl ester, the succinate of which has a melting point of 83-84°C and which has an optical rotation of +14.6° (c=1; water, 20°C, 589 nm), which is the compound of Example 61.

[0022] In accordance with the foregoing, the present invention also provides an agent of the invention, for use as a pharmaceutical, e.g. for the treatment of any condition mentioned above.

[0023] The present invention furthermore provides a pharmaceutical composition comprising an agent of the invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner. Unit dosage forms contain, for example, from about 0.25 to about 150, preferably from about 1 to about 25 mg of a compound according to the invention.

[0024] Moreover the present invention provides the use of an agent of the invention, for the manufacture of a medicament for the treatment of any condition mentioned above.

[0025] The following examples illustrate the invention.

Example 1 : (1-Aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid 1-phenyl-ethyl ester

Imidazole-1-carboxylic acid 1-phenyl-ethyl ester

[0026] To a solution of DL-1-phenylethanol 1.21 ml (10.0 mmol) in 10ml tetrahydrofurane, N,N'-carbonyldiimidazole 1.70 g (10.5 mmol) is added. The white suspension is heated up to 50°C and stirred for 40 minutes at this temperature. The reaction mixture is cooled and evaporated. The crude product is purified by flash chromatography (hexane / ethyl acetate 80 / 20) to yield the title product as colorless oil.

(1-Azu-bicyclo[2.2.2]oct-3-yl)-carbamic acid 1-phenyl-ethyl ester

[0027] To a solution of imidazole-1-carboxylic acid 1-phenyl-ethyl ester 0.50 g (2.31 mmol) in 5 ml dimethylformamide, 3-aminoquinuclidine dihydrochloride 0.46 g (2.31 mmol) and sodium carbonate 0.49 g (4.62 mmol) are added. The suspension is heated up to 80 °C and stirred for 18 hours at this temperature. The reaction mixture is then cooled and extracted with water and ethylacetate. The combined organic phases are dried and evaporated. The oily residue is dried, dissolved in ether and acidified with a 4 M hydrochloric acid dioxane solution. The precipitating crystals are filtered, washed with ether and dried to give the title product. Mp = 71 - 72 °C (decomposition).

Example 2: (1-Aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid benzyl ester

[0028] 3-Aminoquinuclidine dihydrochloride 996 mg (5.0 mmol) is added slowly to a stirred suspension of 676 mg (15.5 mmol) sodium hydride (dispersion 55%) in dimethylformamide (15 ml). Thereafter the suspension is stirred for another 90 minutes at room temperature and then carbobenzoxy chloride 0.72 ml (5.1 mmol) is added slowly. After another two hours at room temperature, the suspension is quenched by carefully adding water. The solvent is then evaporated at 70 °C / 16 mbar. The residue is taken up in water and ethyl acetate. The organic phase is separated and the water phase two-times re-extracted with ethyl acetate. The combined organic phase is dried and evaporated to give the crude oily product which is taken up in dioxane and 0.72 ml of a 4M hydrochloric acid is added. The precipitating product is recrystallised from dioxane/ether to give the hydrochloride of the title product. Mp=192 - 193 °C.

Example 3 : (R)-(+)-(1-Aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid benzyl ester

[0029] Sodium hydride (dispersion 55%) 0.33 g (7.5 mmol) is washed with petrolether and the solvent is removed by separation (decantation). Then, the sodium hydride is carefully suspended in dimethylformamide (12.5 ml). To this suspension (R)-(+)-3-aminoquinuclidine dihydrochloride 0.50 g (2.5 mmol) is added. The initially exothermic reaction is then stirred at room temperature for one hour and then carbobenzoxy chloride 0.39 ml (2.75 mmol) is added to the reaction mixture within 15 minutes. The again initially exothermic reaction is stirred at room temperature for 90 minutes, then the mixture is poured into 10% brine (NaCl/water solution) and then four-times extracted with toluene. The combined organic phases are dried and evaporated. The crude oily residue is dissolved in dioxane (5 ml) and 0.31 ml of a 4 M hydrochloric acid is added. The mixture is then stirred at room temperature till the product precipitates. The crystals are filtered, washed with dioxane and ether and dried to give the title product. Mp = 228 - 229 °C. Optical rotation +6.3 ° (c=0.5, water).

Example 4: (S)-(-)-(1-Aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid benzyl ester

[0030] Sodium hydride (dispersion 55%) 0.33 g (7.5 mmol) is washed with petrolether and the solvent is removed by separation (decantation). Then, the sodium hydride is carefully suspended in dimethylformamide (12.5 ml). To this suspension (S)-(-)-3-aminoquinuclidine dihydrochloride 0.50 g (2.5 mmol) is added. The initially exothermic reaction is then stirred at room temperature for one hour and then carbobenzoxy chloride 0.39 ml (2.75 mmol) is added to the reaction mixture within 15 minutes. The again initially exothermic reaction is stirred at room temperature for 90 minutes then the mixture is poured into 10% brine (NaCl/water solution) and then four-times extracted with toluene. The combined organic phases are dried and evaporated. The crude oily residue is dissolved in dioxane (5 ml) and 0.31 ml of a 4 M hydrochloric acid is added. The mixture is then stirred at room temperature till the product precipitates. The crystals are filtered, washed with dioxane and ether and dried to give the title product. Mp = 221 - 223 °C. Optical rotation -8.0 ° (c=0.5, water).

Example 5: (1-Aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid 4-butyl-benzyl ester

[0031] Triethylamine 1.05 ml (7.5 mmol) and 0.80 g di-(N-succinimidyl)carbonate are added to a solution of (4-butyl-phenyl)methanol 0.47 ml (2.75 mmol) in 15 ml dichloromethane. The initial suspension is stirred at room temperature for 45 minutes to become a clear solution. This mixture is added dropwise to a solution of 3-aminoquinuclidine 0.32 g (2.5 mmol) and 0.52 ml (1.5 mmol) triethylamine in 10 ml dichloromethane. The reaction mixture is subsequently stirred for another two hours at room temperature. Afterwards the mixture is washed with 20 ml water. The organic phase is separated, dried and evaporated. The crude product is dissolved in 5 ml dichloromethane and acidified with a saturated solution of hydrochloric acid in ether. By addition of 50 ml ether a white product precipitates. The crystals are filtered, washed with ether and dried to give the title product. Mp = 174 - 175°C (decomposition).

[0032] The following compounds of formula I wherein n is 2, R_1 and R_2 are hydrogen and A is a substituted phenyl group can be prepared in analogy to Examples 1, 2 or 5.

Example	R_3	R_4	R_5	Mp / Optical Rotation
6	H	o-OMe	H	89-90°C (hydrochloride)
7	H	2-OMe	3-OMe	93-95°C (hydrochloride)
8	H	p-phenyl	H	193-195°C (hydrochloride)
9	H	o-Br	H	203-204°C (hydrochloride)
10	H	o-NO_2	H	177-178°C (hydrochloride)
11	H	p-NO_2	H	89-90°C (hydrochloride)
12	H	2-OMe	5-Br	147-149°C (hydrochloride)
13	H	m-phenoxy	H	82-83°C (hydrochloride)
14	H	o-Cl	H	82-83°C (hydrochloride)
15	H	3-NO_2	5-NO_2	93-94°C (hydrochloride)
16	H	3-Cl	4-Cl	*
17	H	m-OMe	H	139-140°C (hydrochloride)
18	H	3-NO_2	4-Me	86-88°C (hydrochloride)
19	H	3-Me	5-Me	183-184°C (hydrochloride)
20	H	p-CF_3	H	143-144°C (hydrochloride)
21	H	o-Me	H	174-176°C (hydrochloride)
22	H	p-Me	H	194-196°C (hydrochloride)
23	H	p-isopropyl	H	235°C (hydrochloride)
24	Me	p-Me	H	168-170°C (hydrochloride)

Me = Methyl

* IS: Carbonyl absorption at 1695 cm^{-1}

(continued)

Example	R_3	R_4	R_5	Mp / Optical Rotation
25 cis/trans racemic mixture	Me	H	H	71-72 °C (hydrochloride)
26 Stereoiso mer-1	Me	H	H	182-184 °C (hydrochloride) ; optical rotation: + 32.4 ° (c=1; water, 24 °C, 589 nm)
27 Stereoiso mer-2	Me	H	H	151-152 °C (succinate) optical rotation: - 9.7 ° (c=1; methanol, 22 °C, 589 nm)
28 Stereoiso mer-3	Me	H	H	optical rotation: + 12.5 ° (c=1; methanol, 20 °C, 589 nm)
29 Stereoiso mer-4	Me	H	H	117-119 °C (fumarate) optical rotation: - 25.0 ° (c=1; methanol, 20 °C, 589 nm)
30	H	3-OMe	5-OMe	179-180 °C (hydrochloride)
31	H	3-Me	4-NO_2	165-167 °C (hydrochloride)
32	Me	2-Cl	4-Cl	212-214 °C (hydrochloride)
33	H	p-Ethyl	H	208-209 °C (hydrochloride)
34	H	p-Br	H	190-191 °C (hydrochloride)
35	H	3-CF_3	5-CF_3	157-158 °C (hydrochloride)
36	H	p-SMe	H	164-166 °C (hydrochloride)
37	H	2-NO_2	5-Me	198-199 °C (hydrochloride)
38	H	3-OMe	4-OMe	221-223 °C (hydrochloride)
39	H	2-Cl	6-Cl	251-252 °C (hydrochloride)
40	H	p-CO_2Me	H	220-222 °C (hydrochloride)
41	Me	p-tButyl	H	232-233 °C (hydrochloride)
42	Ethyl	H	H	**
43	Me	p-Cl	H	132-135 °C (hydrochloride)
44	Me	o-Me	H	219-220 °C (hydrochloride)
45	Me	p-Br	H	163-165 °C (hydrochloride)
46	Me	3-Cl	4-Cl	240-241 °C (hydrochloride)
47	Me	p-F	H	219-220 °C (hydrochloride)
48	H	m-Br	H	186-187 °C (hydrochloride)
49	H	m-Me	H	174-175 °C (hydrochloride)
50	H	m-OBenzyl	H	168-169 °C (hydrochloride)
51	H	2-Cl	5-Cl	205-207 °C (hydrochloride)
52	H	2-OMe	5-OMe	162-163 °C (hydrochloride)
53	H	2-NO_2	4-Cl	204-205 °C (hydrochloride)
54 cis/trans racemic mixture	Me	o-Cl	H	230-232 °C (hydrochloride)
55 Stereoiso mer-1	Me	o-Cl	H	229-230 °C (hydrochloride) optical rotation: - 8.6 ° (c=1; water, 20 °C, 589 nm)
56 Stereoiso mer-2	Me	o-Cl	H	255-257 °C (hydrochloride) optical rotation: + 26.8 ° (c=1; water, 22 °C, 589 nm)

** IS: Carbonyl absorption at 1712 cm^{-1}

(continued)

Example	R_3	R_4	R_5	Mp / Optical Rotation
57 Stereoiso mer-3	Me	o-Cl	H	229-230 °C (hydrochloride) optical rotation: + 8.9 ° (c=1; water, 20 °C, 589 nm)
58 Stereoiso mer-4	Me	o-Cl	H	257-258 °C (hydrochloride) optical rotation: - 30.9 ° (c=1; water, 22 °C, 589 nm)
59 Stereoiso mer-1	Me	o-F	H	83-84 °C (succinate) optical rotation: + 15.4 ° (c=1; water, 20 °C, 589 nm)
60 Stereoiso mer-2	Me	o-F	H	146-147 °C (succinate) optical rotation: + 2.5 ° (c=1; water, 20 °C, 589 nm)
61 Stereoiso mer-3	Me	o-F	H	83-84 °C (succinate) optical rotation: + 14.6 ° (c=1; water, 20 °C, 589 nm)
62 Stereoiso mer-4	Me	o-F	H	136-137 °C (succinate) optical rotation: - 4.8 ° (c=1; water, 20 °C, 589 nm)

Example 63: (1-Aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid benzo[1,3]dioxol-5-ylmethyl ester

[0033] Prepared in analogy to example 1, 2 or 5.
Mp (hydrochloride) = 186-187°C.

Example 64: (1-Aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid benzo[1,3]dioxol-4-nitro-5-ylmethyl ester

[0034] Prepared in analogy to example 1, 2 or 5.
Mp (hydrochloride) = 216-218 °C.

Example 65: (1-Aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid 3,4,5-trimethoxy-benzyl ester

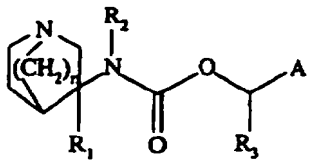
[0035] Prepared in analogy to example 1, 2 or 5.
Mp (hydrochloride) = 211-212 °C.

Example 66 1-Aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid benzo[1,2,5]thiadiazol-5-ylmethyl ester

[0036] Prepared in analogy to example 1, 2 or 5.
IS: Carbonyl absorption at 1718 cm^{-1}

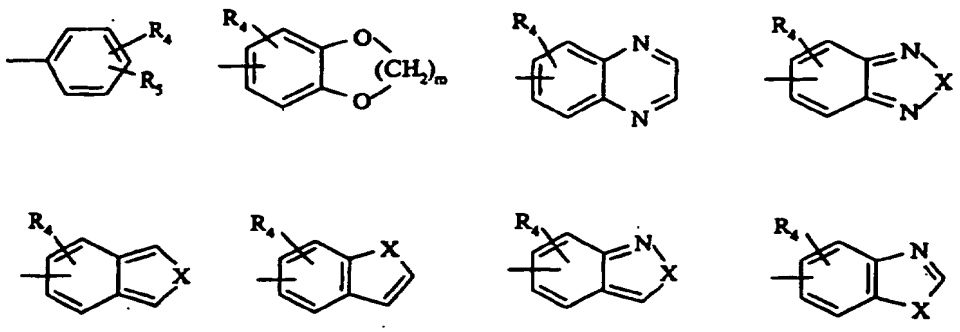
Claims

1. A compound of formula I



I

wherein n is 1 or 2, R_1, R_2 and R_3, independently, are hydrogen or (C_{1-4})alkyl and A is a group of formula

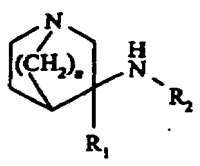


wherein m is 1, 2 or 3, X is O, S, NH or CH_2 and R_4 and R_5, independently, are hydrogen, halogen, hydroxy, (C_{1-4}) alkyl, (C_{1-4})alkoxy, (C_{1-4})alkylthio, (C_{1-4})alkylamino, nitro, trifluoromethyl or phenyl, in free base or acid addition salt form.

2. A compound according to claim 1 which is a stereoisomer of the (1-azabicyclo[2.2.2]oct-3-yl)carbamic acid 1-(2-fluorophenyl)-ethyl ester, in free base or acid addition salt form.

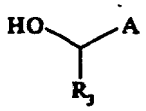
3. A compound according to claim 1 which is the stereoisomer of the (1-azabicyclo[2.2.2]oct-3-yl)-carbamic acid 1-(2-fluorophenyl)-ethyl ester, the succinate of which has a melting point of 83-84°C and which has an optical rotation of +14.6° (c=1; water, 20°C, 589 nm), in free base or acid addition salt form.

4. A process for the preparation of a compound of formula I as defined in claim 1, or a salt thereof, which comprises the step of reacting a compound of formula II



II

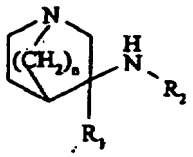
wherein n, R_1 and R_2 are as defined in claim 1, with a compound of formula III



III

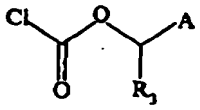
wherein R_3 and A are as defined in claim 1, and N, N'-carbonyldiimidazole or di(N-succinimidyl)carbonate, and recovering the resulting compound of formula I in free base or acid addition salt form.

5. A process for the preparation of a compound of formula I as defined in claim 1, or a salt thereof, which comprises the step of reacting a compound of formula II



II

wherein n, R_1 and R_2 are as defined in claim 1, with a compound of formula IV



IV

wherein R_3 and A are as defined above, and recovering the resulting compound of formula I in free base or acid addition salt form.

6. A compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.

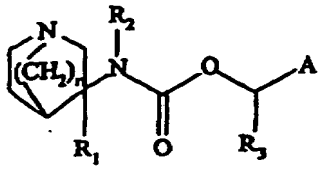
7. A compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for use in the treatment of psychotic and neurodegenerative disorders.

8. A pharmaceutical composition comprising a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

9. The use of a compound of claim 1 in free base or pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the treatment of psychotic and neurodegenerative disorders.

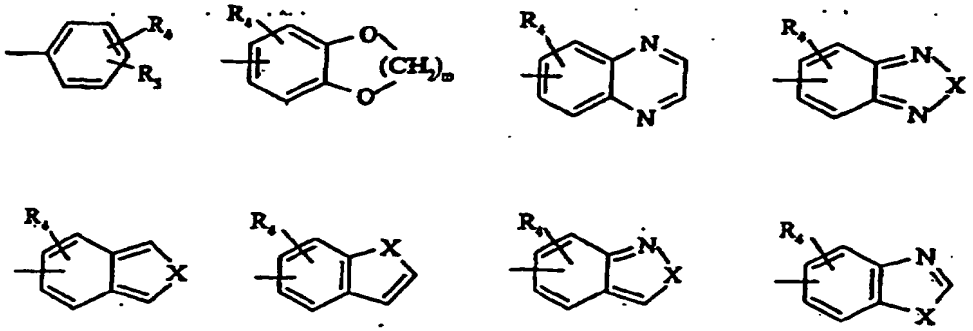
Patentansprüche

1. Verbindung der Formel I



I

worin n für 1 oder 2 steht, R_1, R_2 und R_3 unabhängig für Wasserstoff oder C_1-C_4 Alkyl stehen und A für eine Gruppe der Formeln steht

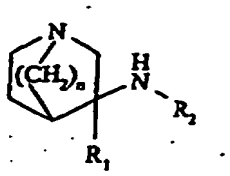


worin m für 1, 2 oder 3 steht, X für O, S, NH oder CH_2 steht und R_4 und R_5 unabhängig für Wasserstoff, Halogen, Hydroxy, C_1-C_4 Alkyl, C_1-C_4 Alkoxy, C_1-C_4 Alkylthio, C_1-C_4 Alkylamino, Nitro, Trifluormethyl oder Phenyl stehen, in Form der freien Base oder in Säureadditionssalzform.

2. Verbindung nach Anspruch 2, die ein Stereoisomer des (1-Aza-bicyclo[2.2.2]oct-3-yl)carbaminsäure-1-(2-fluorphenyl)ethylesters in Form der freien Base oder in Säureadditionssalzform ist.

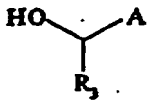
3. Verbindung nach Anspruch 1, die das Stereoisomer des (1-Aza-bicyclo[2.2.2]oct-3-yl)carbaminsäure-1-(2-fluorphenyl)ethylesters ist, dessen Succinat einen Schmelzpunkt von 83-84°C aufweist und das eine optische Drehung von +14,6° (c = 1, Wasser, 20°C, 589 nm) aufweist, in Form der freien Base oder in Säureadditionsalzform.

4. Verfahren zur Herstellung einer Verbindung der Formel I nach Anspruch 1 oder eines Salzes hiervon, das den Schritt der Umsetzung einer Verbindung der Formel II



II

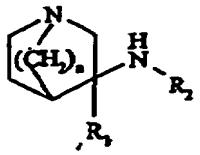
worin n, R_1 und R_2 wie in Anspruch 1 definiert sind, mit einer Verbindung der Formel m,



III

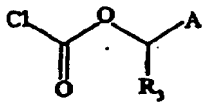
worin R_3 und A wie in Anspruch 1 definiert sind, und N,N'-Carbonyldiimidazol oder Di-(N-succinimidyl)carbonat und der Gewinnung der entstehenden Verbindung der Formel I in Form der freien Base oder in Säureadditionssalzform umfasst.

5. Verfahren zur Herstellung einer Verbindung der Formel I nach Anspruch 1 oder eines Salzes hiervon, das den Schritt der Umsetzung einer Verbindung der Formel II



II

worin n, R_1 und R_2 wie in Anspruch 1 definiert sind, mit einer Verbindung der Formel IV



IV

worin R_3 und A wie oben definiert sind, und der Gewinnung der entstehenden Verbindung der Formel I in Form der freien Base oder in Säureadditionssalzform umfasst.

6. Verbindung nach Anspruch 1 in Form der freien Base oder in pharmazeutisch annehmbarer Säureadditionssalzform zur Verwendung als Pharmazeutikum.

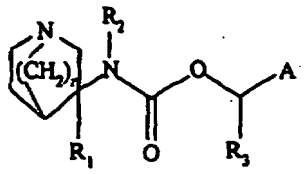
7. Verbindung nach Anspruch 1 in Form der freien Base oder in pharmazeutisch annehmbarer Säureadditionssalzform zur Verwendung bei der Behandlung von psychotischen und neurodegenerativen Störungen.

8. Pharmazeutische Zusammensetzung, die eine Verbindung nach Anspruch 1 in Form der freien Base oder in pharmazeutisch annehmbarer Säureadditionssalzform zusammen mit einem pharmazeutischen Träger oder Verdünnungsmittel umfasst.

9. Verwendung einer Verbindung nach Anspruch 1 in Form der freien Base oder in pharmazeutisch annehmbarer Säureadditionssalzform zur Herstellung eines Arzneimittels zur Behandlung von psychotischen und neurodegenerativen Störungen.

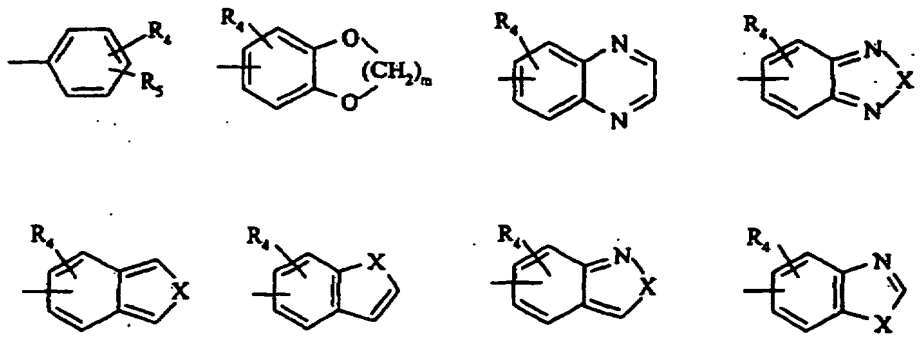
Revendications

1. Composé de formule I :



I

dans laquelle n vaut 1 ou 2, R_1, R_2 et R_3 représentent indépendamment l'hydrogène ou un groupe alkyle en C_1 à C_4, et A est un groupe de formule :

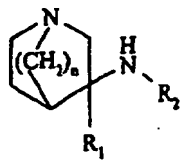


dans laquelle m vaut 1, 2 ou 3, X représente O, S, NH ou CH_2, et R_4 et R_5 représentent indépendamment l'hydrogène, un halogène, un groupe hydroxy, alkyle en C_1 à C_4, alcoxy en C_1 à C_4, alkylthio en C_1 à C_4, alkyle en C_1 à C_4-amino, nitro, trifluorométhyle ou phényle, sous forme d'un base libre ou d'un sel d'addition d'acide.

2. Composé suivant la revendication 1, qui est un stéréoisomère de l'ester 1-(2-fluorophényl)éthylique de l'acide (1-aza-bicyclo[2.2.2]oct-3-yl)-carbamique, sous forme de base libre ou sous forme d'un sel d'addition d'acide.

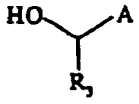
3. Composé suivant la revendication 1, qui est le stéréoisomère de l'ester 1-(2-fluorophényl)éthylique de l'acide (1-aza-bicyclo[2.2.2]oct-3-yl)-carbamique, dont le succinate a un point d'ébullition de 83-84°C et une rotation optique de +14,6° (c=1 ; eau, 20 °C, 589 nm), sous forme de base libre ou sous forme d'un sel d'addition d'acide.

4. Procédé de préparation d'un composé de formule I tel que défini dans la revendication 1, ou d'un de ses sels, qui comprend l'étape consistant à amener à réagir un composé de formule II :



II

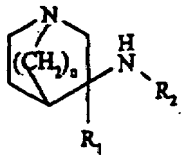
dans laquelle n, R_1 et R_2 sont tels que définis dans la revendication 1, avec un composé de formule III :



III

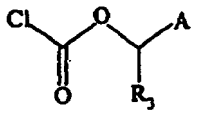
dans laquelle R_3 et A sont tels que définis dans la revendication 1, et le N,N'-carbonyldiimidazole ou le carbonate de di-(N-succinimidyle), et à récupérer le composé résultant de formule I sous forme de base libre ou sous forme d'un sel d'addition d'acide.

5. Procédé de préparation d'un composé de formule I tel que défini dans la revendication 1, ou d'un de ses sels, qui comprend l'étape consistant à amener à réagir un composé de formule II :



II

dans laquelle n, R_1 et R_2 sont tels que définis dans la revendication 1, avec un composé de formule IV :



IV

dans laquelle R_3 et A sont tels que définis ci-dessus, et la récupération du composé de formule I sous forme de base libre ou sous forme d'un sel d'addition d'acide.

6. Composé suivant la revendication 1 sous forme de base libre ou sous forme d'un sel d'addition d'acide pharmaceutiquement acceptable, à utiliser comme médicament.

7. Composé suivant la revendication 1 sous forme de base libre ou sous forme d'un sel d'addition d'acide pharmaceutiquement acceptable, à utiliser dans le traitement de troubles psychotiques et neurodégénératifs.

8. Composition pharmaceutique comprenant un composé suivant la revendication 1 sous forme de base libre ou sous forme d'un sel d'addition d'acide pharmaceutiquement acceptable, en association avec un support ou diluant pharmaceutique.

9. Utilisation d'un composé suivant la revendication 1 sous forme de base libre ou sous forme d'un sel d'addition d'acide pharmaceutiquement acceptable, pour la fabrication d'un médicament pour le traitement de troubles psychotiques et neurodégénératifs.